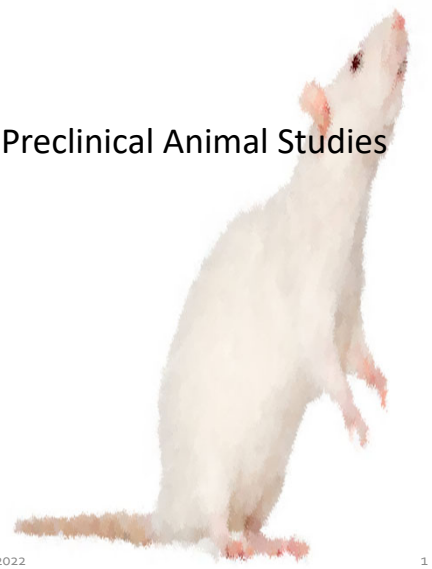
Improving nonclinical research practices: way forward

2022. LAS webinar series organized by CroLASA in collaboration with SLAS



Experimental Design and Reproducibility in Preclinical Animal Studies

Aurora Brønstad,
University of Bergen/ESLAV
May 11th, 2022

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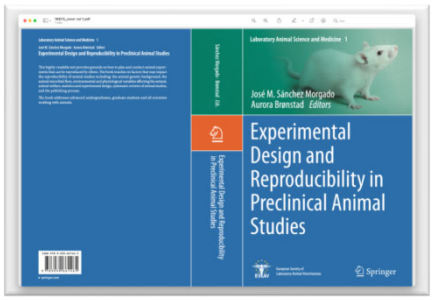


Aurora Brønstad

Chief veterinarian – Faculty of medicine – University of Bergen - NORWAY

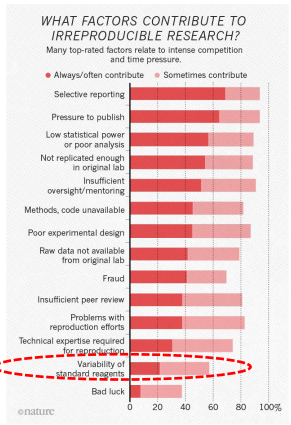
- Veterinary surgeon, Oslo 1995 – Companion animal practice full/part-time 1995-2003
- PhD Physiology at University of Bergen 2004
- Chief veterinarian at University of Bergen (1999-20xx)

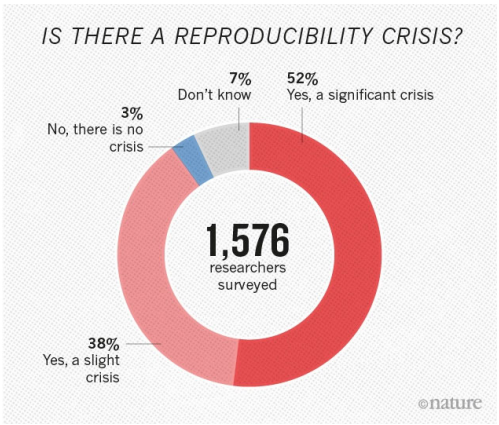
- Member of Scand-LAS board (2002-2008)
- COST B24 Laboratory animal science and welfare 2004-2009
- AALAS - FELASA working group on harm-benefit analysis of animal studies (2011-2016)
- AAALAC ad hoc 2011-2016
- AAALAC Council board (2016-xx)
- **President ESLAV (2017-2019)**
- Co-Editor ESLAV Series **Laboratory Animal Science and Medicine 1:** Experimental Design and Reproducibility in Preclinical Animal Studies – published September 2021
- FELASA 2022 – Scientific Committee

2

3

Scientific Scepticisme - Reproducilibilty





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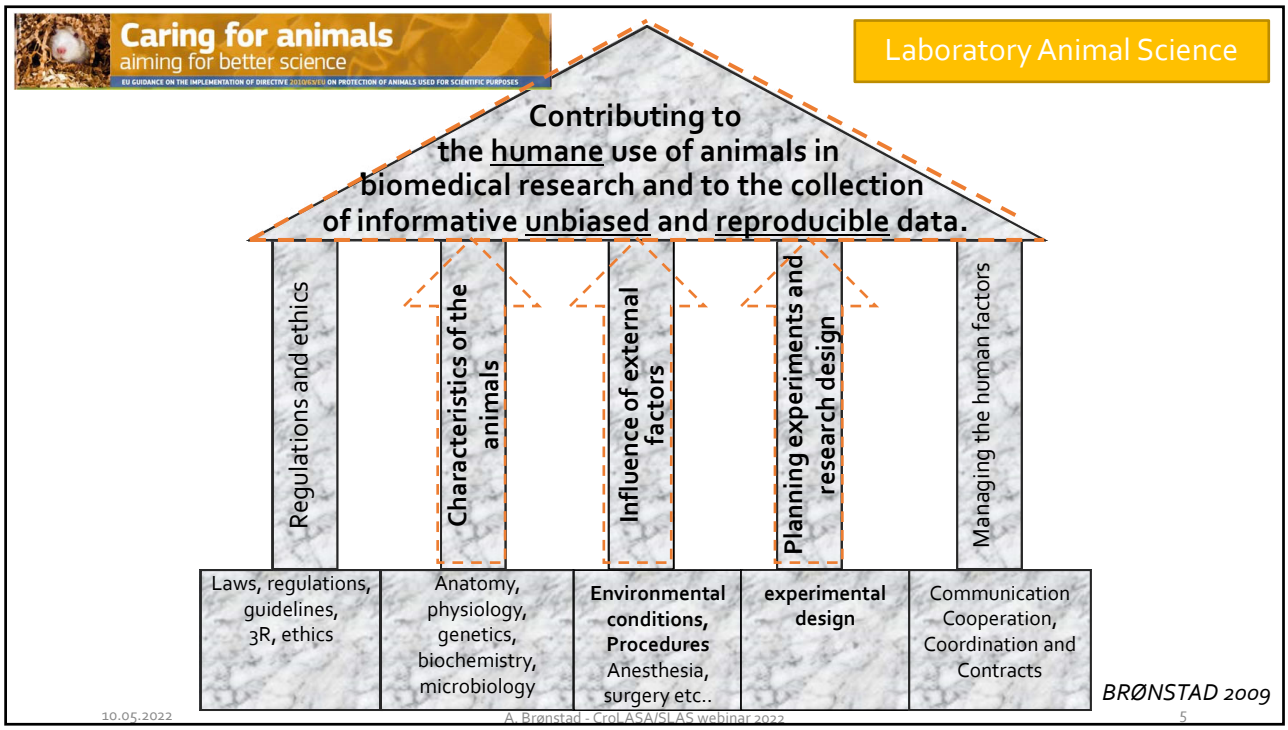

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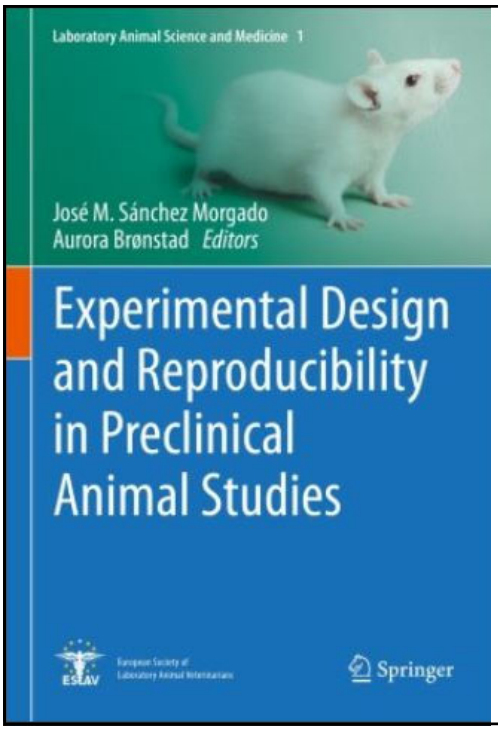
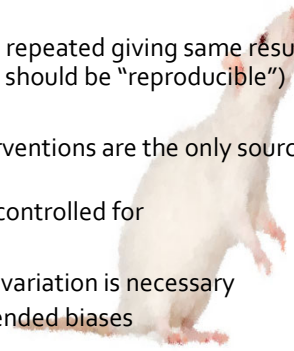


Reproducibility

- Experiments should be repeated giving same results any place at any time (they should be "reproducible")
  - Experimental interventions are the only source of difference
  - Everything else is controlled for
  - Strict control with variation is necessary
  - Be aware of unintended biases



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Part I:
The Animal and the Environment
5/10/2022
A. Brønstad - CroLASA/SLAS webinar 2022
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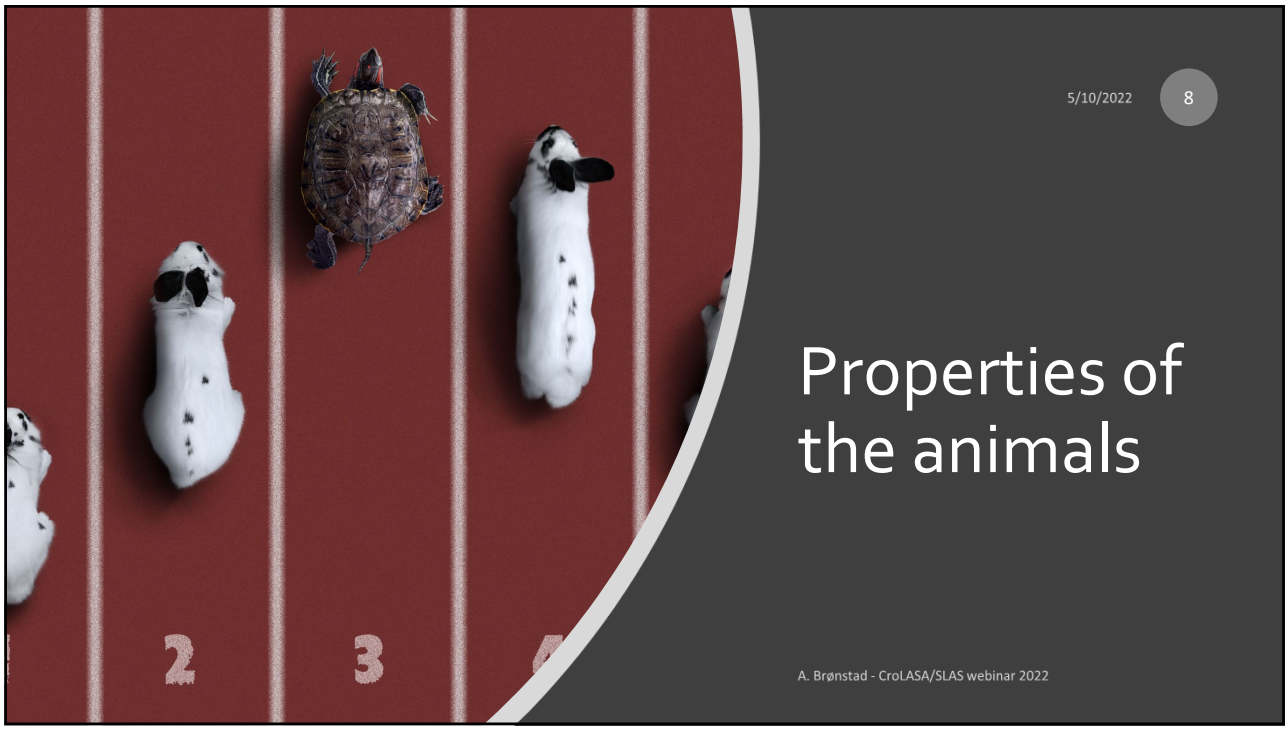
5/10/2022
8
Properties of the animals
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8

https://www.jax.org/strain/

Also Known As:B6, B6/J
C57BL/6J is the most widely used inbred strain and the first to have its genome sequenced.

- Refractory to many tumors
- Background for maximal expression of most mutations
- Resistant to audiogenic seizures,
- Have relatively low bone density
- Develop age related hearing loss

Susceptible to diet-induced obesity, type 2 diabetes, and atherosclerosis. Macrophages from this strain are resistant to the effects of anthrax lethal toxin.

Also Known As:B6N, Black 6N
This is an NIH subline of C57BL/6 separated from C57BL/6J in 1951.

Five SNP differences have been identified that distinguish C57BL/6J from C57BL/6ByJ and C57BL/6NJ.

This strain does not have the deletion in the *Nnt* gene that has been found in the C57BL/6J strain

Also Known As:B6 albino, albino B6
B6(Cg)-*Tyr*$^{c-2J}$/J, or B6-albino mice, are **C57BL/6J mice that carry a mutation in the tyrosinase gene.**

Pigment is completely absent from skin, hair and eyes in mice homozygous for *Tyr*$^{c-2J}$.

- Ideal for creation of novel strains with targeted mutations

9

Rodent Genetics

Fernando Benavides and Jean-Louis Guénet

- Genetic variability
  - introduction to mammalian genetics
  - overview of the main standardized strains
  - genetically modified animals
  - genetic monitoring
  - rodent phenotyping.

Genetic background
Genetic drift

https://www.jax.org/strain/

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Properties of the environment
5/10/2022
A. Brønstad - CroLASA/SLAS webinar 2022
11

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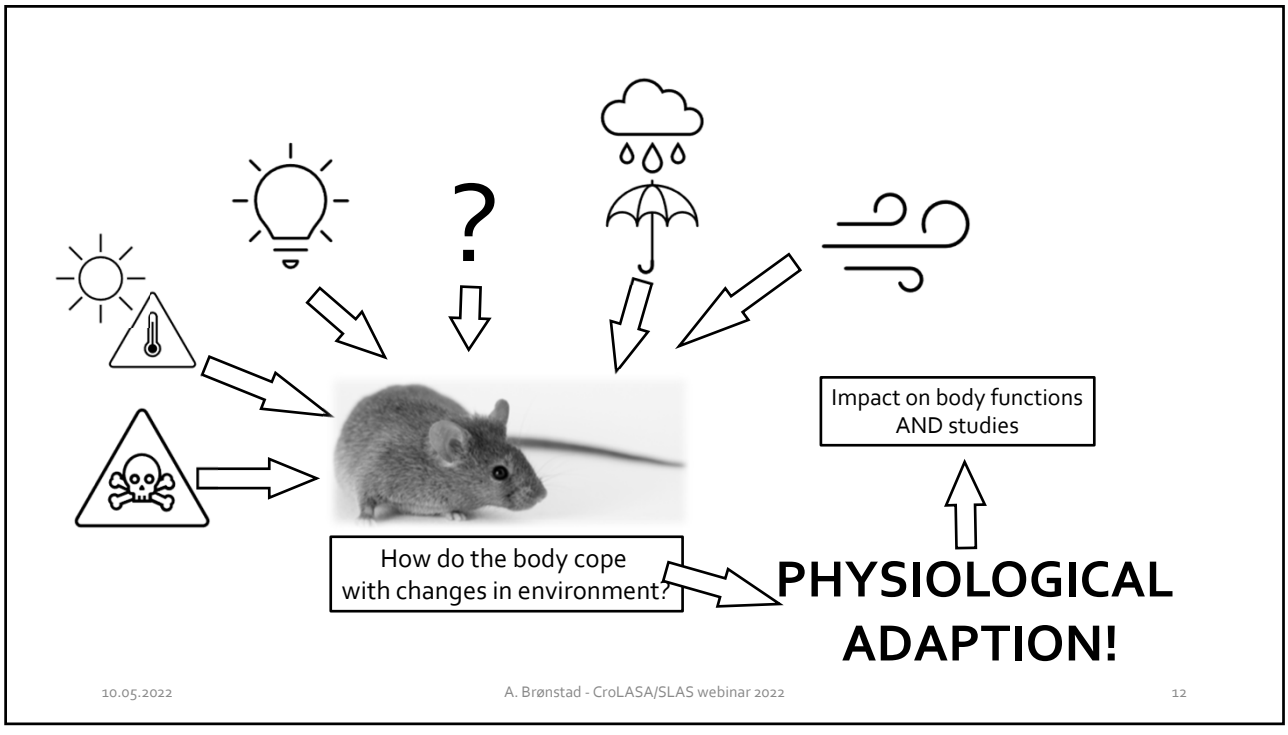
?
Impact on body functions AND studies
How do the body cope with changes in environment?
PHYSIOLOGICAL ADAPTION!
10.05.2022
A. Brønstad - CroLASA/SLAS webinar 2022
12

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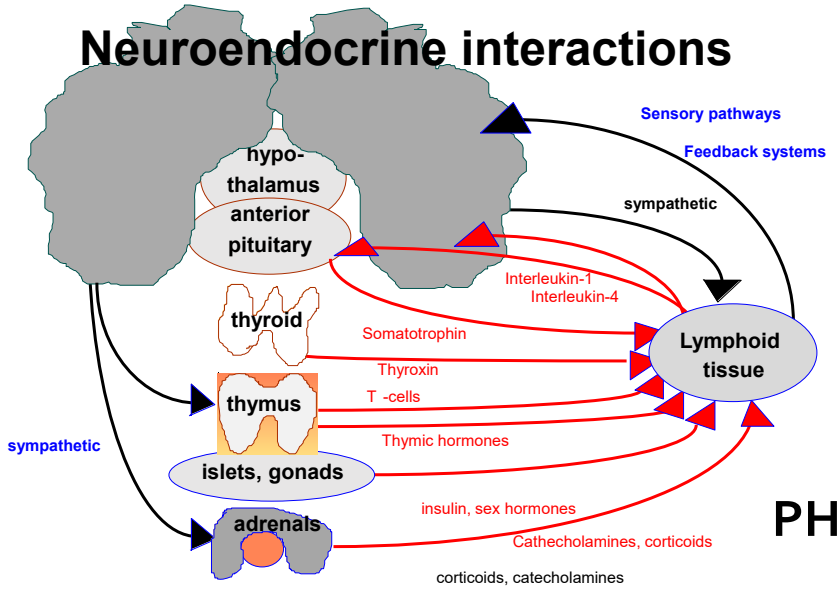
Neuroendocrine interactions



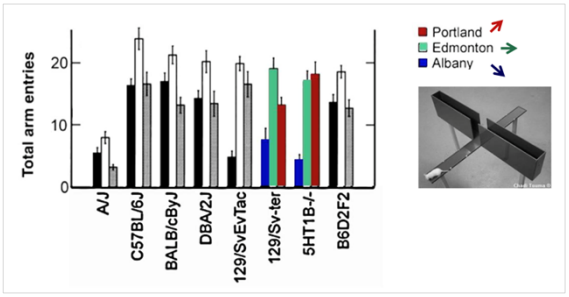
COMPLEX SYSTEM

PHYSIOLOGICAL ADAPTION!

13

Properties of animals AND environment

14



REPORT

Genetics of Mouse Behavior: Interactions with Laboratory Environment

John C. Crabbe[1,*], Douglas Wahlsten[2], Bruce C. Dudek[3]
+ See all authors and affiliations

Science 04 Jun 1999:
Vol. 284, Issue 5420, pp. 1670-1672
DOI: 10.1126/science.284.5420.1670

Article | Figures & Data | Info & Metrics | eLetters | PDF

Abstract

Strains of mice that show characteristic patterns of behavior are critical for research in neurobehavioral genetics. Possible confounding influences of the laboratory environment were studied in several inbred strains and one null mutant by simultaneous testing in three laboratories on a battery of six behaviors. Apparatus, test protocols, and many environmental variables were rigorously equated. Strains differed markedly in all behaviors, and despite standardization, there were systematic differences in behavior across labs. For some tests, the magnitude of genetic differences depended upon the specific testing lab. Thus, experiments characterizing mutants may yield results that are idiosyncratic to a particular laboratory.

https://science.sciencemag.org/content/284/5420/1670.long

15

Biological variation AND Experimental design

16

Control of biologic variation

17

Control Experiment

Control of biologic variation

Pairwise comparison

⇩

Reduction of animal number

✚

More information per animal

18

Theory in Biosciences (2021) 140:169–176
https://doi.org/10.1007/s12064-021-00340-y

ORIGINAL ARTICLE

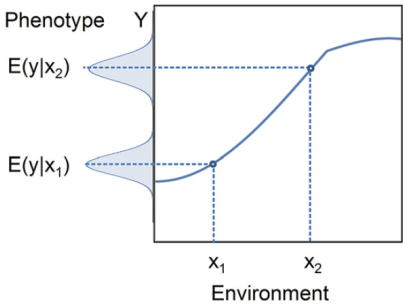
A reaction norm perspective on reproducibility

Bernhard Voelkl[1] · Hanno Würbel[1]

Received: 7 January 2019 / Accepted: 1 March 2021 / Published online: 25 March 2021

Abstract
Reproducibility in biomedical research, and more specifically in preclinical animal research, has been seriously questioned. Several cases of spectacular failures to replicate findings published in the primary scientific literature have led to a perceived reproducibility crisis. Diverse threats to reproducibility have been proposed, including lack of scientific rigour, low statistical power, publication bias, analytical flexibility and fraud. An important aspect that is generally overlooked is the lack of external validity caused by rigorous standardization of both the animals and the environment. Here, we argue that a reaction norm approach to phenotypic variation, acknowledging gene-by-environment interactions, can help us seeing reproducibility of animal experiments in a new light. We illustrate how dominating environmental effects can affect inference and effect size estimates of studies and how elimination of dominant factors through standardization affects the nature of the expected phenotype variation through the reaction norms of small effect. Finally, we discuss the consequences of reaction norms of small effect for statistical analysis, specifically for random effect latent variable models and the random lab model.

Theory in Biosciences (2021) 140:169–176



19

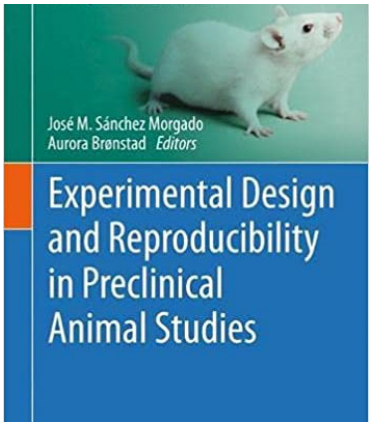
Properties of the Design of Experiments AND Environment ANDBiology

20

Light – impact on experiments

- In general, lighting should be diffused throughout an animal holding area and provide sufficient illumination for the animals' well-being while permitting good housekeeping practices and adequate animal inspection
  - In reality, light is a compromise between optimality for animals and people who work with them
  - Identical lighting in the whole room is often difficult
- Light intensity decreases with the square of the distance from its source.
- Light intensity may differ as much as 80-fold in transparent cages from the top to the bottom of a rack
- **Location of a cage on a rack affects the intensity of light to which the animals within are exposed**

Design of experiments
Randomisation

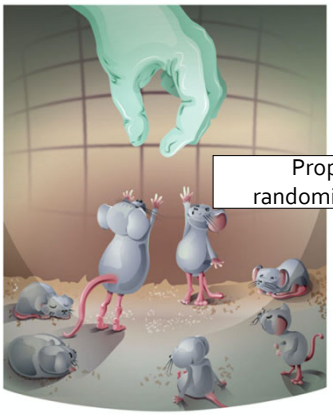


Systematic Reviews

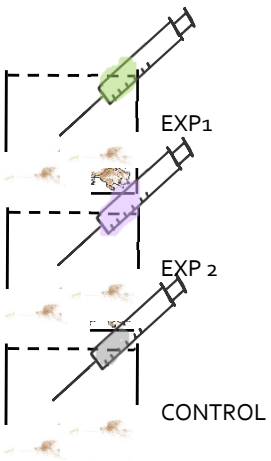
Janet Becker Rodgers and Merel Ritskes-Hoitinga

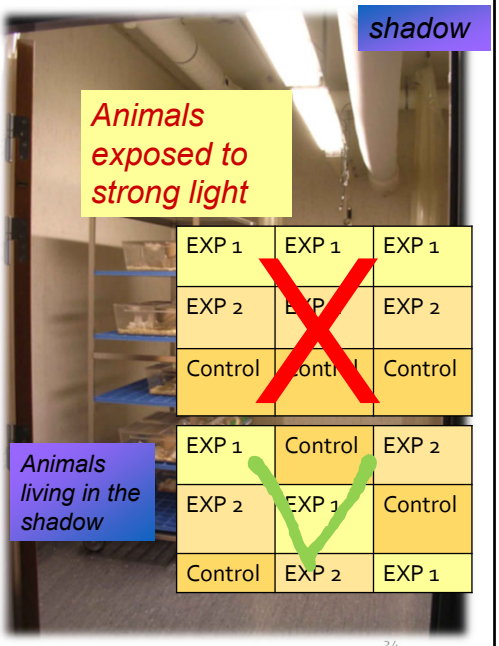
Fig. 5 Simply reaching for the first mouse that can be caught in a cage is not random (V. Altounian/*Science*) [103]. Used with permission

RANDOMISATION IN THE CAGES
AND ON THE ON THE RACK



Proper randomization





PREPARE Guidelines

Experimental Design and Reproducibility in Preclinical Animal Studies pp 263–277 | Cite as

Planning Animal Experiments

Adrian J. Smith

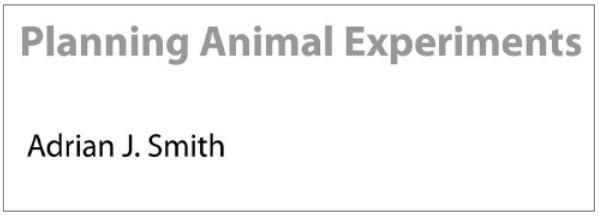
Chapter | First Online: 01 September 2021

322 Accesses

Part of the Laboratory Animal Science and Medicine book series (LASM,volume 1)

Abstract

Despite efforts to improve the planning of animal experiments by better reporting, there is still great room for improvement. Many scientists appear to be unaware of the impact which apparently insignificant routines in an animal facility can have on their experiments, and they rely upon the facility staff to take care of these. The same applies to the more mundane aspects of their research such as handling, injection techniques and blood sampling. The aim of this chapter is to demonstrate the need for close collaboration between scientists and facility staff from day 1 of the planning process. This collaboration will have a win-win effect: improving experimental design, implementing the three Rs, optimising animal welfare and safeguarding all of those affected, directly or indirectly, by the research. The chapter underlines the importance of advice and checklists for planning animal research and testing, such as those embodied in the PREPARE guidelines.



Planning Animal Experiments

Adrian J. Smith

Original Article https://journals.sagepub.com/doi/full/10.1177/0023677217724823

Laboratory Animals
2018, Vol. 52(2) 135–141
! The Author(s) 2017
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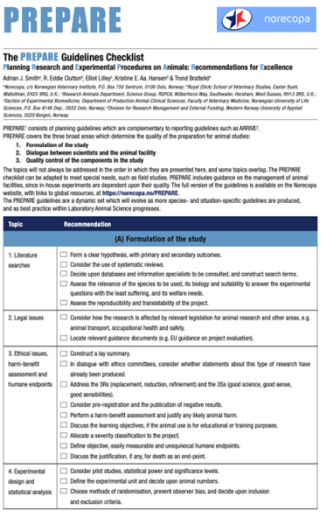
PREPARE: guidelines for planning animal research and testing

Adrian J Smith[1], R Eddie
Kristine E Aa Hansen[4] and

Abstract

There is widespread concern ab
animals. Although there are a n
ance on how to *plan* animal expe
In this paper we present the
on Animals: Recommendations
the quality of the preparation f
facility, and quality control of th
checklist should be adapted to s
list is available on the Norecopa
norecopa.no/PREPARE.



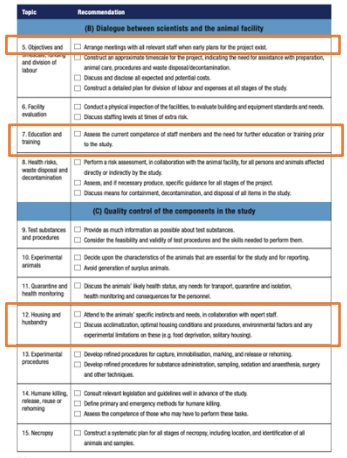
PREPARE

norecopa

The PREPARE Guidelines Checklist

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

Topic	Recommendation
(A) Formulation of the study	
1. Literature searches	☐ Form a clear hypothesis, with primary and secondary outcomes. ☐ Consider the use of systematic reviews. ☐ Decide upon databases and information specialists to be consulted, and construct search terms. ☐ Assess the relevance of the species to be used, its biology and suitability to answer the experimental questions with the least suffering, and its welfare needs. ☐ Assess the reproducibility and translatability of the project.
2. Legal issues	☐ Consider how the research is affected by relevant legislation for animal research and other areas, e.g. animal transport, occupational health and safety. ☐ Locate relevant guidance documents (e.g. EU guidance on project evaluation).
3. Ethical issues, harm-benefit assessment and humane endpoints	☐ Construct a lay summary. ☐ In dialogue with ethics committees, consider whether statements about this type of research have already been produced. ☐ Address the 3Rs (replacement, reduction, refinement) and the 3Ss (good science, good sense, good sensibilities). ☐ Consider pre-registration and the publication of negative results. ☐ Perform a harm-benefit assessment and justify any likely animal harm. ☐ Discuss the learning objectives, if the animal use is for educational or training purposes. ☐ Allocate a severity classification to the project. ☐ Define objective, easily measurable and unequivocal humane endpoints. ☐ Discuss the justification, if any, for death as an end-point.
4. Experimental design and statistical analysis	☐ Consider pilot studies, statistical power and significance levels. ☐ Define the experimental unit and decide upon animal numbers. ☐ Choose methods of randomisation, prevent observer bias, and decide upon inclusion and exclusion criteria.



Topic	Recommendation
(B) Dialogue between scientists and the animal facility	
5. Objectives and timescales, sharing and division of labour	☐ Arrange meetings with all relevant staff when early plans for the project exist. ☐ Construct an approximate timescale for the project, indicating the need for assistance with preparation, animal care, procedures and waste disposal/decontamination. ☐ Discuss and disclose all expected and potential costs. ☐ Construct a detailed plan for division of labour and expenses at all stages of the study.
6. Facility evaluation	☐ Conduct a physical inspection of the facilities, to evaluate building and equipment standards and needs. ☐ Discuss staffing levels at times of extra risk.
7. Education and training	☐ Assess the current competence of staff members and the need for further education or training prior to the study.
8. Health risks, waste disposal and decontamination	☐ Perform a risk assessment, in collaboration with the animal facility, for all persons and animals affected directly or indirectly by the study. ☐ Assess, and if necessary produce, specific guidance for all stages of the project. ☐ Discuss means for containment, decontamination, and disposal of all items in the study.
(C) Quality control of the components in the study	
9. Test substances and procedures	☐ Provide as much information as possible about test substances. ☐ Consider the feasibility and validity of test procedures and the skills needed to perform them.
10. Experimental animals	☐ Decide upon the characteristics of the animals that are essential for the study and for reporting. ☐ Avoid generation of surplus animals.
11. Quarantine and health monitoring	☐ Discuss the animals' likely health status, any needs for transport, quarantine and isolation, health monitoring and consequences for the personnel.
12. Housing and husbandry	☐ Attend to the animals' specific instincts and needs, in collaboration with expert staff. ☐ Discuss acclimatization, optimal housing conditions and procedures, environmental factors and any experimental limitations on these (e.g. food deprivation, solitary housing).
13. Experimental procedures	☐ Develop refined procedures for capture, immobilisation, marking, and release or rehoming. ☐ Develop refined procedures for substance administration, sampling, sedation and anaesthesia, surgery and other techniques.
14. Humane killing, release, reuse or rehoming	☐ Consult relevant legislation and guidelines well in advance of the study. ☐ Define primary and emergency methods for humane killing. ☐ Assess the competence of those who may have to perform these tasks.
15. Necropsy	☐ Construct a systematic plan for all stages of necropsy, including location, and identification of all animals and samples.

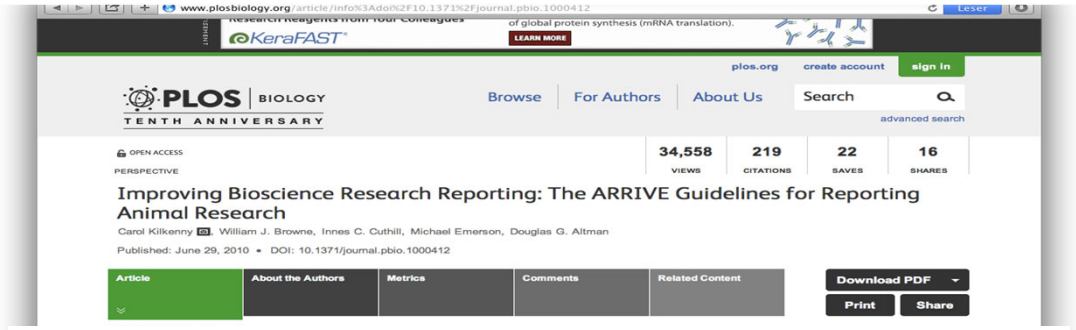
References

1. Smith AJ, Clutton RE, Lilley E, Hansen KEA & Brattelid T. PREPARE Guidelines for Planning Animal Research and Testing. *Laboratory Animals*. 2017. DOI: 10.1177/0023677217724823.
2. Kilkenny C, Browne WJ, Cuthill IC *et al.* Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. *PLoS Biology*. 2010; DOI: 10.1371/journal.pbio.1000412.

Further information
https://norecopa.no/PREPARE | post@norecopa.no | @norecopa

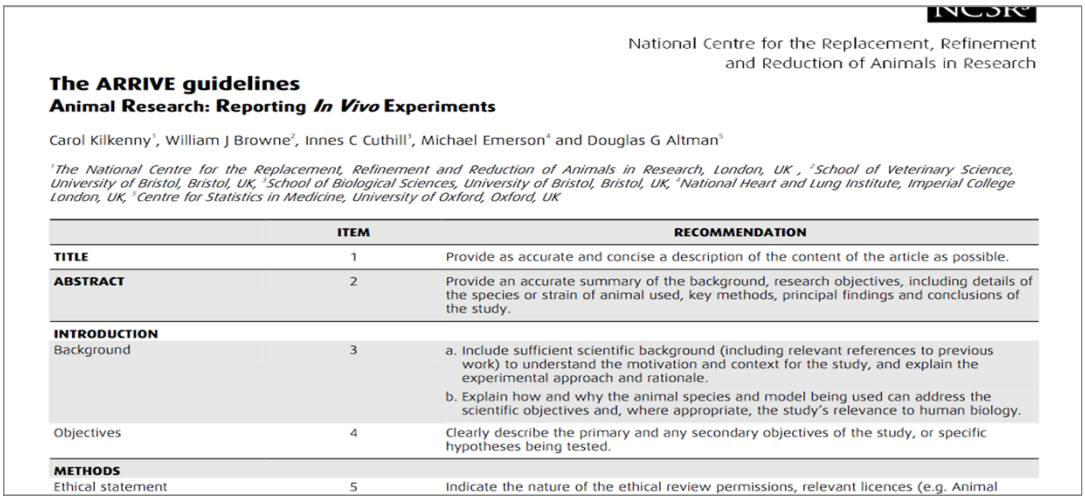
Arabic
Simplified Chinese
Czech
Danish
Dutch
English
Finnish
French
German
Greek
Bahasa Indonesia
Italian
Japanese
Korean
Latvian
Norwegian
Persian (Farsi)
Polish
Portuguese
Portuguese (Brazilian)
Russian
Spanish
Swedish
Thai
Turkish

http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1000412



The ARRIVE (Animal Research: Reporting *In Vivo* Experiments) guidelines are intended to improve the reporting of animal experiments. Published in the journal PLoS Biology and eleven other journals

http://cdn.elsevier.com/promis_misc/ARRIVE.pdf



National Centre for the Replacement, Refinement and Reduction of Animals in Research

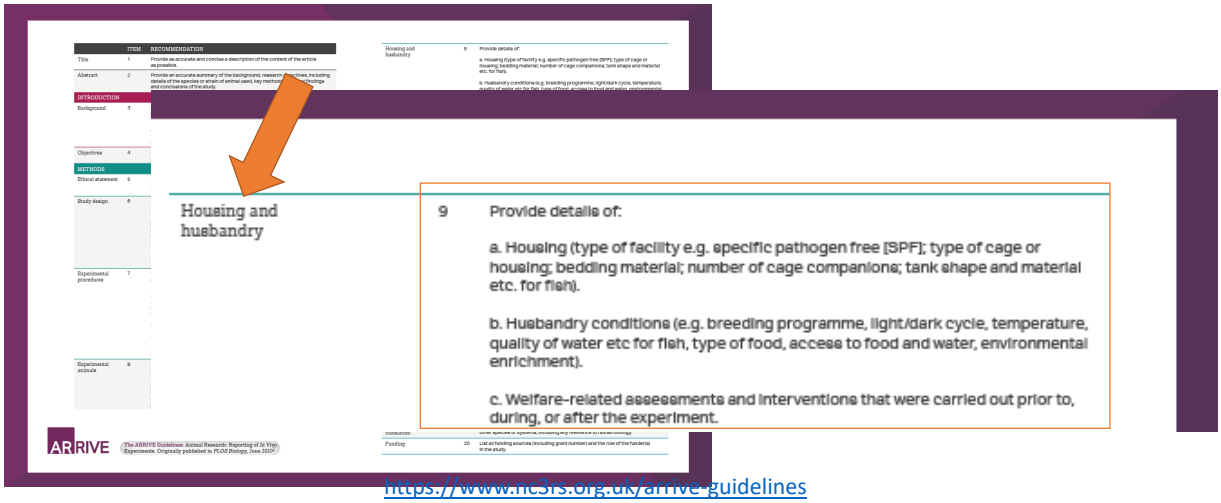
The ARRIVE guidelines
Animal Research: Reporting *In Vivo* Experiments

Carol Kilkenny[1], William J Browne[2], Innes C Cuthill[3], Michael Emerson[4] and Douglas G Altman[5]

[1]*The National Centre for the Replacement, Refinement and Reduction of Animals in Research, London, UK*, [2]*School of Veterinary Science, University of Bristol, Bristol, UK*, [3]*School of Biological Sciences, University of Bristol, Bristol, UK*, [4]*National Heart and Lung Institute, Imperial College London, UK*, [5]*Centre for Statistics in Medicine, University of Oxford, Oxford, UK*

	ITEM	RECOMMENDATION
TITLE	1	Provide as accurate and concise a description of the content of the article as possible.
ABSTRACT	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.
INTRODUCTION		
Background	3	a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale. b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.
METHODS		
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal

ARRIVE guidelines for reporting animal studies



Housing and husbandry

9 Provide details of:

a. Housing (type of facility e.g. specific pathogen free [SPF]; type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish).

b. Husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, quality of water etc for fish, type of food, access to food and water, environmental enrichment).

c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.

https://www.nc3rs.org.uk/arrive-guidelines

Experimental Design and Reproducibility in Preclinical Animal Studies pp 185–211 | C

Scholarly Publishing and Scientific Reproducibility

Arieh Bomzon & Graham Tobin

Chapter | First Online: 01 September 2021

334 Accesses

Part of the Laboratory Animal Science and Medicine book series (LASM,volume 1)

Abstract

Poor quality of reporting in published scientific manuscripts has been identified as a major contributor to the low reproducibility of research outcomes. Improved author compliance to a journal's submission guidelines, rigorous editorial vigilance by competent reviewers and journal editors, and revamped research practices and policies by research institutes can raise the reporting quality of submitted manuscripts. In this chapter, we describe the current requirements of scholarly publishing and the responsibilities of authors, peer reviewers, journal editors, scientific journals, and academic institutions. We propose that scientific reproducibility can be improved by (a) upgrading editorial vigilance to assure the quality and accuracy of the scientific record; (b) institutional training in writing in the sciences for research trainees; and (c) institutional adoption of existing standards of quality control in manufacturing and commercial research organizations to develop good publishing and research practices and integrity.

Scholarly Publishing and Scientific Reproducibility

Arieh Bomzon and Graham Tobin

- Good reporting
  - accuracy, transparency, and the efficient transfer of knowledge.
  - provision of sufficient information to other researchers in the field to reproduce, replicate, or repeat published findings.
  - Independent and unbiased
- The process of Scholary publishing
  - Reporing Guideliens
  - External Peer review
  - Dissemination

Hypothesis generation

Plannin a study

What is a hypothesis?

A hypothesis is a logical supposition, a reasonable guess, an educated conjecture. It provides a tentative explanation for a phenomenon under investigation." (Leedy and Ormrod, 2001).

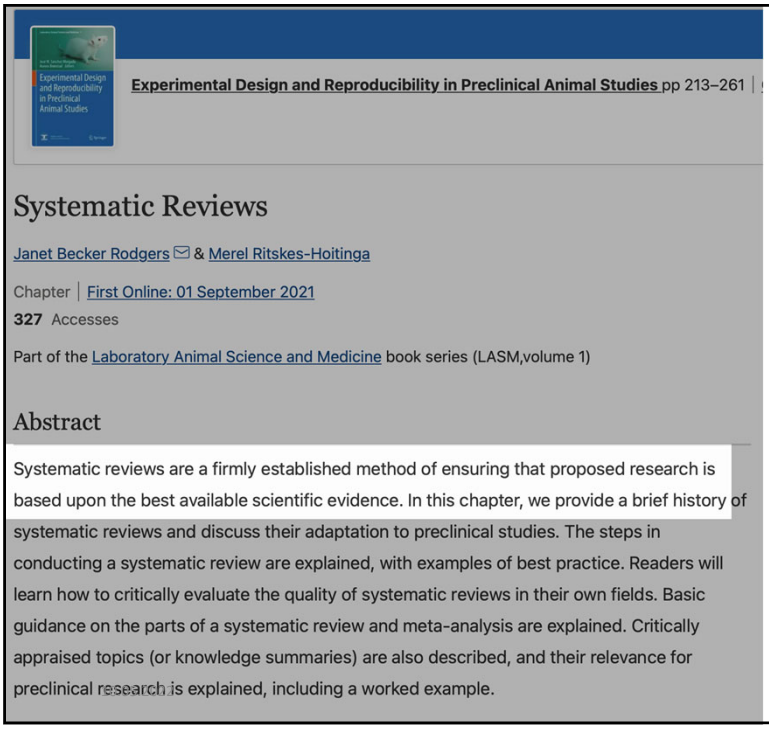
By formulating a series of reasonable guesses of cause and effect we are able to understand and explore the events in our surrounding environment (Leedy and Ormrod, 2001)

A hypothesis is important because it guides the research. An investigator may refer to the hypothesis to direct his or her thought process toward the solution of the research problem or subproblems. The hypothesis helps an investigator to collect the right kinds of data needed for the investigation. Hypotheses are also important because they help an investigator to locate information needed to resolve the research problem or subproblems (Leedy and Ormrod, 2001).

http://people.uwec.edu/piercech/ResearchMethods/Generating%20a%20research%20hypothesis/generating%20a%20research%20hypothesis%20index.htm

"Collect the
right kinds of data needed for the investigation"

"guides the research"



Experimental Design and Reproducibility in Preclinical Animal Studies pp 213–261

Systematic Reviews

Janet Becker Rodgers & Merel Ritskes-Hoitinga

Chapter | First Online: 01 September 2021

327 Accesses

Part of the Laboratory Animal Science and Medicine book series (LASM,volume 1)

Abstract

Systematic reviews are a firmly established method of ensuring that proposed research is based upon the best available scientific evidence. In this chapter, we provide a brief history of systematic reviews and discuss their adaptation to preclinical studies. The steps in conducting a systematic review are explained, with examples of best practice. Readers will learn how to critically evaluate the quality of systematic reviews in their own fields. Basic guidance on the parts of a systematic review and meta-analysis are explained. Critically appraised topics (or knowledge summaries) are also described, and their relevance for preclinical research is explained, including a worked example.

Systematic Reviews

Janet Becker Rodgers and Merel Ritskes-Hoitinga

Systematic Reviews

Janet Becker Rodgers and Merel Ritskes-Hoitinga

Fig. 1 Archie Cochrane at his home, ca 1956 [18]

- Brief history of research synthesis
- What is a systematic review
- Systematic review of animal studies
- How systematic review inform Preclinical Science
- Validity
  - Internal and external validity
- Formal procedure of a systematic review (step by step)
  - Team
  - Specify the research question to answer
  - Databases and sources of information
  - Data extraction
  - Risk of Bias- evaluation
  - Blinding
  - Randomization
  - Meta analysis
  - Graphic presentation – Forest plots and Funnel plots

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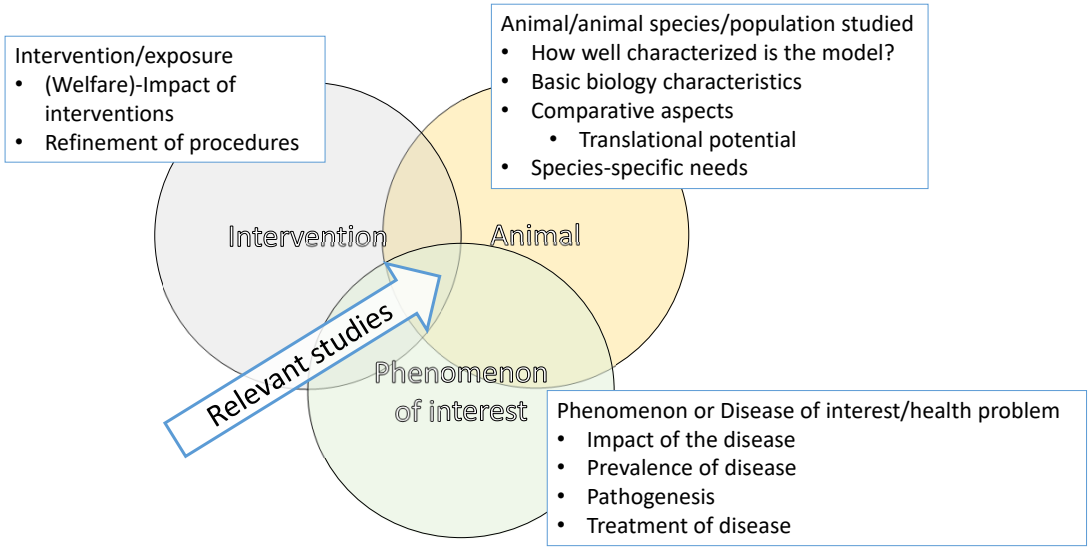
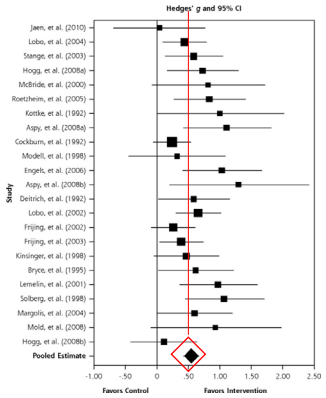
10.05.2022

Search components

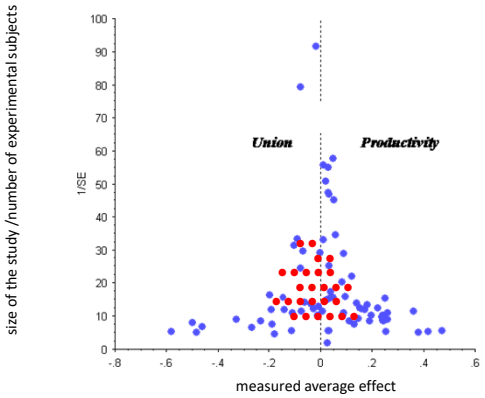


Meta-analysis

forest plot



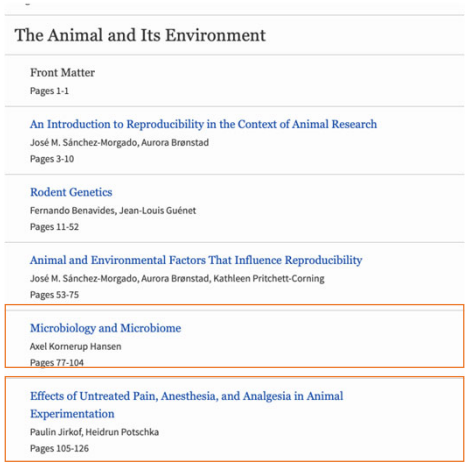
funnel plot

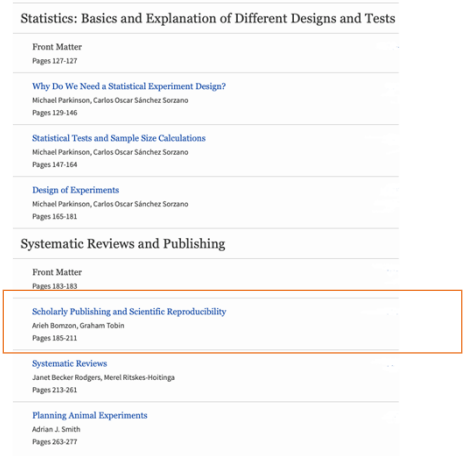


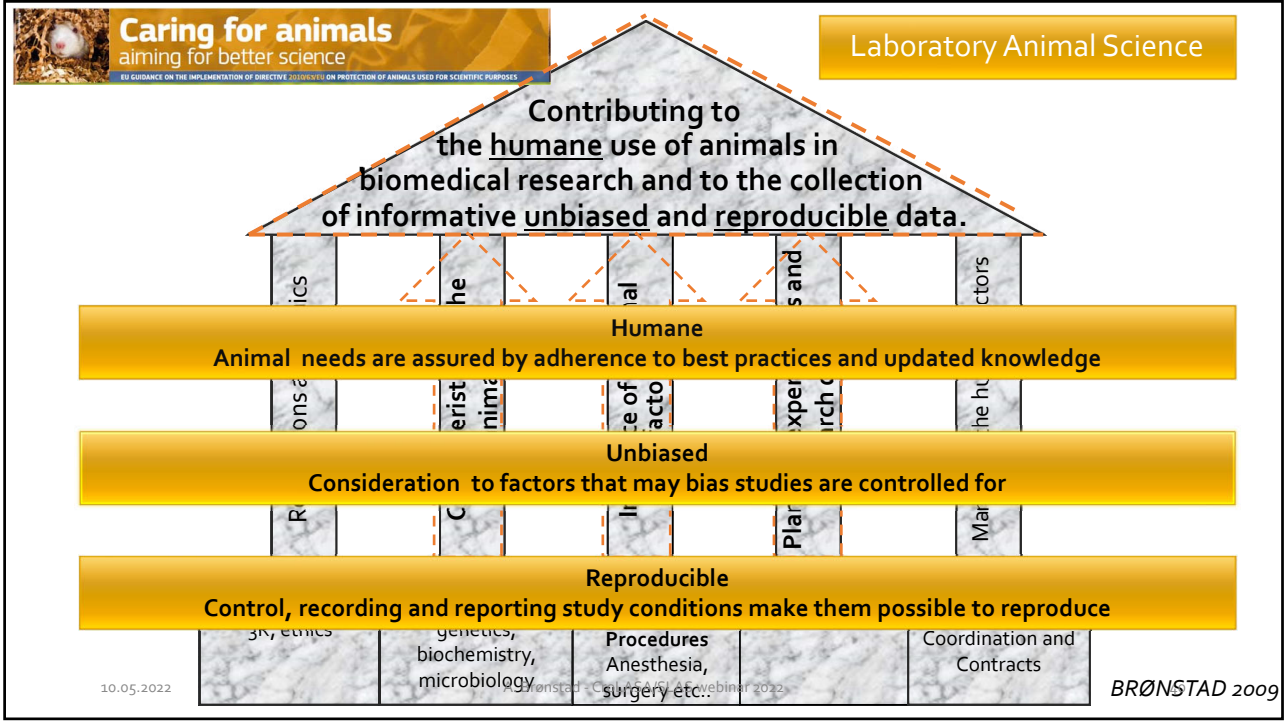
Søren Kierkegaard *(Danish philosopher)*

- *"Alle vil Udvikling – ingen vil Forandring"*
- *«everyone wants development – nonone like change»*

Experimental Design and Reproducibility in Preclinical Animal Studies







ESLAV EDUCATIONAL OPTIONS

EUROPEAN SOCIETY OF LABORATORY ANIMAL VETERINARIANS

ESLAV/ECLAM Summer and Winter School

Summer School takes place once a year in the Summer. Consists of 5 Modules, which are repeated. Please visit the events' pages for updated information.

- Diseases & Diagnostics
- Biology of Laboratory Animals
- Management of Animal Facilities, Ethics, Animal Welfare and 3Rs
- Surgery and Experimental Techniques, Design and conduct of research programmes & animal experiments
- Pre-anaesthesia, Anaesthesia, Analgesia, and Euthanasia

Winter School consists of more advanced topics that are selected every year. Please visit the events' pages for updated information.

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2022 Webinars

"How does conventional rodent housing affect animals' health and longevity?" Prof. Georgia Mason, Campbell Centre for the Study of Animal Welfare, University of Guelph, Canada. Friday, February 11, 2022 - Stockholm 3 PM CET ~ Webinar recording ~ pdf file

"Preregistration of animal studies: why and how" Julia Menon, Daily Director, preclinicaltrials.eu Friday, February 18, 2022 - Stockholm 1 PM CET

"Choice of laboratory rodent diet may confound data interpretation and reproducibility" Dr. Michael Pellizzon, Research Diets Inc, NJ, U.S. Friday, March 18, 2022, Stockholm 3 PM CET ~ Webinar recording ~ pdf file

"Is this a harmful phenotype? How to responsibly assess genetically induced phenotypes in rodents" Dr. Anne Zintzsch, Animal Welfare Officer, University of Basel, Switzerland. Friday, April 1, 2022 × Stockholm 1 PM CET ~ Webinar recording ~ pdf file ~ shared materrial during the presentation: Compilation of severity classifications across Europe ~ Info about the International Mouse Phenotyping Consortium (IMPC).

"Humane endpoints for mice" Elizabeth Nunamaker, Director of Animal Welfare, Charles River Laboratory, U.S. Friday, April 8, 2022 × Stockholm 2 PM CET ~ Webinar recording ~ pdf file ~ answers to the questions

"The standardization fallacy in animal research – and how to avoid it" Prof. Hanno Würbel, Animal Welfare Division, Veterinary Public Health Institute, University of Bern, Switzerland. Friday, April 29, 2022 × Stockholm 1 PM CET Register here (by Apr 27)

Recommended reading:

- Voelkl, B. and Würbel, H. 2021. A reaction norm perspective on reproducibility. Theory Biosci. 140, 169–176.
- B Voelkl, L Vogt, E Sena, H Würbel 2018. Reproducibility of preclinical animal research improves with heterogeneity of study samples. PLOS Biol., 16(2), e2003693.
- Voelkl, B., Altman, N.S., Forsman, A., Forstmeier, W., Gurevitch, J., Jaric, I., Karp, N.A., Kas, M.J., Schielzeth, H., Van de Casteele, T., Würbel, H. 2020. Reproducibility of animal research in light of biological variation. Nat. Rev. Neurosci. 21, 384–393.
- Voelkl, B. and Würbel, H. 2021. A reaction norm perspective on reproducibility. Theory Biosci. 140, 169–176.

"What exactly is 'N' in animal experiments?" Stanley E. Lazic, Prioris.ai Inc., Ottawa, Canada Friday, May 6, 2022 × Stockholm 2 PM CET Register here (by May 4)

Further reading: What exactly is 'N' in cell culture and animal experiments? Lazic SE *et al.* 2018.

"NEXT LEVEL REFINEMENTS: Perioperative practices in rodent medicine" Claire Hankenson, Associate Vice Provost for Research and Executive Director of University Laboratory Animal Resources, University of Pennsylvania, U.S. Wednesday, May 18, 2022 × Stockholm 2 PM CET Register here (by May 17)

"Challenges in project evaluation in animal research" Matthias Eggel, Institute for Philosophy, University of Basel, Switzerland Friday, June 3, 2022 × Stockholm 1 PM CET Register here (by Jun 1)

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